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Case Report

Recurrent Blocked Duct(s) in a Mother with Immunoglobulin A Deficiency

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Abstract

Secretory immunoglobulin A (sIgA) is the dominant immunoglobulin in human milk, and apart from the obvious contribution it makes towards the protection of the infant, sIgA may also form an important part of the defense of the mammary gland. This report involves a mother (M8) who participated in a research study investigating the relationships between symptoms and changes in the physiology of the lactating breast during mastitis. Breastmilk samples were collected on Days 14, 30, 60, and 90 postpartum, to establish the normal reference range of biochemical markers, and during periods of breast inflammation. M8 experienced seven episodes of blocked duct(s) during the first 19 weeks, five of which occurred within the 90-day reference sample collection period. On analysis, it was found there was no detectable sIgA present in her milk samples. Medical referral and further testing resulted in a diagnosis of selective IgA deficiency, of which the mother had not been previously aware. M8 showed little variation in her milk composition even when suffering with blocked duct(s), although there was an increase in the concentration of lactoferrin in both breasts at reference collection days 14–90. Lactoferrin concentration was also unusually high at Day 14 (15 g/L) in the left breast and continued to be increased in this breast until Day 60. The absence of sIgA in this mother's breastmilk may have been a contributing factor in her experiencing recurrent blocked ducts.

Introduction

SECRETORY IMMUNOGLOBULIN (Ig) A (sIgA) is the dominant Ig in human milk with a concentration in colostrum of approximately 10 g/L, which decreases rapidly to 1–2 g/L by the end of the first week after birth.[1] It is a polymeric molecule composed of two (or more) IgA monomers, a J chain, and a secretory component. The important contribution that sIgA makes towards the protection of the neonate is well known[2]; however, it also forms an important part of the defense against pathogens that colonize and invade all body surfaces that are bathed in secretions. It functions by neutralizing bacterial enzymes and toxins and inhibiting bacterial adhesion through the prevention of both nonspecific and stereochemical interactions. It is also thought to act synergistically with innate immune factors present in secretions such as lactoferrin, lactoperoxidase, and mucins.[3] Although there is a paucity of literature specifically regarding the role of sIgA in defense of the mammary gland, there is an abundance of research regarding its effects on the limitation of bacterial adherence in buccal, intestinal, urinary, genital, nasal, and bronchial epithelia.[3]

The importance of the IgA system in protection of the mammary gland is implicated in research involving the stimulation of local immunity in a variety of animals with differing IgA milk levels. The production of local antibodies in the mammary glands of animals infused with antigens was much greater and persisted longer in animals that previously had higher levels of milk IgA.[4] In women, sIgA, in conjunction with lactoferrin and complement 3, was significantly lower in the milk of Gambian women who later developed mastitis.[5] These findings were maintained even when analysis was adjusted for stage of lactation, season, and parity.

IgA deficiency is defined as either primary or secondary in etiology. Secondary deficiency may be related to a range

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of factors, such as drugs and infections (e.g., rubella, cytomegloviruses, Epstein-Barr virus). Although IgA deficiency is generally considered permanent, occasionally there is spontaneous remission, for instance, when the causal medication is ceased.[6] Several physiological variables, such as psychological stress, intense endurance exercise, and sleep deprivation, have been associated with decreased concentrations of sIgA in saliva, where the concentration of salivary sIgA was inversely related to the level of psychological stress experienced.[7,8] As an increased level of stress has been found to be a risk factor for mastitis in multiparous women who are breastfeeding,[9] it is possible there may be a relationship among increased levels of stress, lower levels of sIgA in breastmilk, and susceptibility to mastitis. However, this is not supported by a study that found sIgA in breastmilk was positively correlated to stress in mothers, where stress was assessed using Cohen's Perceived Stress Scale.[10]

Selective IgA deficiency is the most common form of primary immunodeficiency, with a reported frequency of 1:500 in the Caucasian population.[11] Factors associated with the prevalence of selective IgA deficiency include a family history and the country of origin. In particular, selective IgA deficiency varies significantly across differing ethnic groups where, among healthy blood donors, the prevalence has been reported as ranging from one in 328–633 for those of European ancestry to one in 5,000 in China and one in 18,500 in Japan.[12] Caution in the interpretation of some of these findings has been recommended because of the variation in definitions used in some diagnostic testing.[12] Most laboratories now define the adult reference range as 0.8–4.0 g/L, where deficiency in IgA is defined as <0.07 g/L, which is the concentration below which nephelometry (the routine commercial laboratory test used for Igs) becomes unreliable.[13]

Case Report

This report involves a mother (M8), a Caucasian, 33-year-old primipara, who participated in a research study investigating the relationships between clinical descriptors and changes in the physiology of the lactating breast during mastitis.[14–16] In brief, the study required samples of milk from both breasts and 24-hour urine samples to be collected on Days 5, 14, 30, 60, and 90 postpartum and blood to be collected on Days 5 and 14, to establish the normal reference range of biochemical markers for each individual participant in the cohort. Breastmilk samples were hand-expressed, and a single blood sample was taken at a point during the 24-hour urine collection that was convenient for the mother. Milk samples were analyzed for sodium (Na), chloride (Cl), lactose, glucose, C-reactive protein (CRP), sIgA, lactoferrin, and serum albumin. Urine samples were analyzed for lactose, and blood samples were assayed for lactose and CRP. When women reported inflammatory breast symptoms the researcher visited them in their home daily and again at follow-up, 7 days after resolution of symptoms. During these visits samples of blood, milk from the affected and contralateral breasts, and 24-hour urine specimens were collected. Mothers were interviewed at reference and mastitis time points to establish the presence of any co-existing illness and breast pathology. Hypothesis testing of all outcome measures was based on analyses of variance with repeated measures. All analyses were adjusted for stage of lactation and co-existing breast and systemic pathologies.

Inflammation of the breast during lactation is experienced in differing degrees of severity, and not all episodes of breast inflammation are classified as mastitis. Clinically, milder cases of focal inflammation that are not accompanied by systemic illness are traditionally diagnosed as blocked duct(s).[17] Often these episodes are manifested by a localized area of erythema and tenderness that may be accompanied by a nodular lumpiness on palpation and usually respond to the conservative management of increased frequency of breastfeeding and massage of the affected area.[17]

Blocked duct(s), for the purpose of this study, were defined as localized inflammatory breast symptoms that were present for less than 24 hours with no accompanying systemic symptoms. Localized inflammatory breast symptoms were defined as either focal erythema or tenderness/pain that may or may not be associated with a nodular lumpiness on palpation. During the study period there were 13 episodes of blocked ducts experienced by eight mothers. Eleven of the episodes were accompanied by co-existing pathologies. Three mothers experiencing only one episode each of blocked duct(s) also suffered with either nipple trauma (n = 2) or perceived oversupply (n = 1). Two mothers had diagnosed medical disorders: Hashimoto's thyroiditis and IgA deficiency. The mother with Hashimoto's thyroiditis (M21) experienced four episodes of mastitis late in her lactation (between Day 280 and Day 400) and one episode of blocked duct(s) (Day 310) during a period of significant personal stress. The mean concentration of sIgA in her breastmilk during the 90-day reference sample collection period (0.91 ± 0.15 g/L) was already significantly lower ($t_{22} = 4.9$, $P < 0.001$) than that of the other asymptomatic mothers in the study cohort (1.1 ± 0.5 g/L). The mother (M8) with IgA deficiency is the subject of this case report, and she experienced seven of the 13 observed episodes of blocked duct(s) within the first 19 weeks postpartum.

Results

Despite five of the seven recurrent episodes of blocked duct(s) occurring during the 90-day reference sample collection period, M8 was asymptomatic at each of the routine reference collection days. On analysis, there was no detectable sIgA (detection limit, >0.09 g/L) present in any of her milk samples. As a result, her Day 14 blood sample was sent to an independent commercial laboratory where IgA, IgG, and IgM in blood were analyzed. Normal ranges at this laboratory were stated as follows: IgA, 0.69–3.1 g/L; IgG, 6.1–13 g/L; and IgM, 0.53–3.32 g/L.[18] The results for M8 were <0.0667, 11.3, and 2.92 g/L, respectively, and she was subsequently referred for medical assessment where a diagnosis of selective IgA deficiency was made. M8 had not been previously investigated or diagnosed with IgA deficiency, although she reported multiple and recurrent episodes of sinorespiratory and ear infections as a child, for which surgical interventions were required.

Unfortunately M8 was not recruited into the study until Day 7 postpartum, so there are no Day 5 reference sample results available. Components in the remaining four reference sample collections at Days 14–90 postpartum remained within the normal range for the study cohort,[14] with the ex-

ception of lactoferrin. The concentration of lactoferrin was very high (15 g/L) in her left breast at Day 14 compared to those mothers with asymptomatic breasts (3.8 ± 2.9 g/L), and it remained slightly above the asymptomatic mean for the remaining reference sample collections at Days 30, 60, and 90 postpartum (Fig. 1). The increased concentration of lactoferrin in milk on Day 14 was associated with an elevated serum CRP of 102 mg/L (where the normal CRP in blood is <10 mg/L). There was no evidence of either systemic infection or localized inflammation; however, M8 had experienced a 12-hour labor with no progression of cervical dilatation and meconium-stained liquor and had therefore undergone a nonelective Caesarean section. CRP in milk was undetected, and urinary lactose excretion (4.7 mmol/24 hours) was just outside the normal range for Day 14 (3.4 ± 1.1 mmol/24 hours), perhaps indicating a slight increase in breast permeability.[15]

M8 experienced recurrent blocked duct(s) at Days 35, 36, 65, 68, 72, 114, and 133 postpartum. Episodes were experienced in differing locations of both the right ($n = 4$) and left ($n = 3$) breasts (Fig. 1). Management consisted of frequent feeding, offering the affected breast first, and massage of the affected area, resulting in resolution of symptoms by 24 hours. The only obvious changes that occurred in her milk composition were during episodes experienced at Day 36 and Day 133. During the Day 36 episode both the concentration of Na (12 mmol/L) and Cl (25 mmol/L) in milk from the affected breast were raised, although they did not exceed the normal range from asymptomatic breasts in the study.[14] Milk lactose from the affected breast (176 mmol/L) was within normal range; however, the excretion of lactose in urine was increased (8 mmol/24 hours). During the Day 133 episode, the concentrations of Na (11 mmol/L) and Cl (23 mmol/L) were again raised compared to her reference mean (8.1 and 19.6 mmol/L, respectively), this time in association with a decrease in the concentration of lactose (139 mmol/L) and glucose (0.94 mmol/L). A 24-hour urine specimen was not collected. There were no significant changes in milk composition observed in the remaining five episodes. The lack of change was congruent with the results from the other women with blocked duct(s) whose milk composition and lactose excretion were within normal range for the study sample.[14]

Discussion

Blocked duct(s) are a commonly reported problem among breastfeeding women, and although each episode is generally transient some women can be plagued with many recurrences throughout their lactation. Reassuringly, unlike in mastitis, changes in breastmilk composition are often either absent or short-lived and of little significance,[14] as was the case with M8. During five of the seven episodes of blocked duct(s) her milk composition was within the normal range for the study sample and did not vary greatly from her own asymptomatic reference samples. The variability in milk lactose and the excretion of lactose in urine during the remaining two episodes can perhaps be explained in terms of the differing physiological stages experienced from onset through to recovery of the blocked duct(s) and the timing of the milk and 24-hour urine sample collections. As episodes of blocked ducts are generally of short duration, timing of a single milk sample collection may be crucial to the changes observed, especially in relation to the more encompassing 24-hour urine sample. Changes in milk composition indicative of an increase in paracellular pathway permeability may not be observed as milk from the blocked area may not be able to be expressed. The resulting sample, as on the Day 36 episode, would reflect milk expressed from nonaffected areas of the breast and thus appear within the normal range. However, the concurrent increased excretion of lactose in urine indicates there was an increase in breast permeability

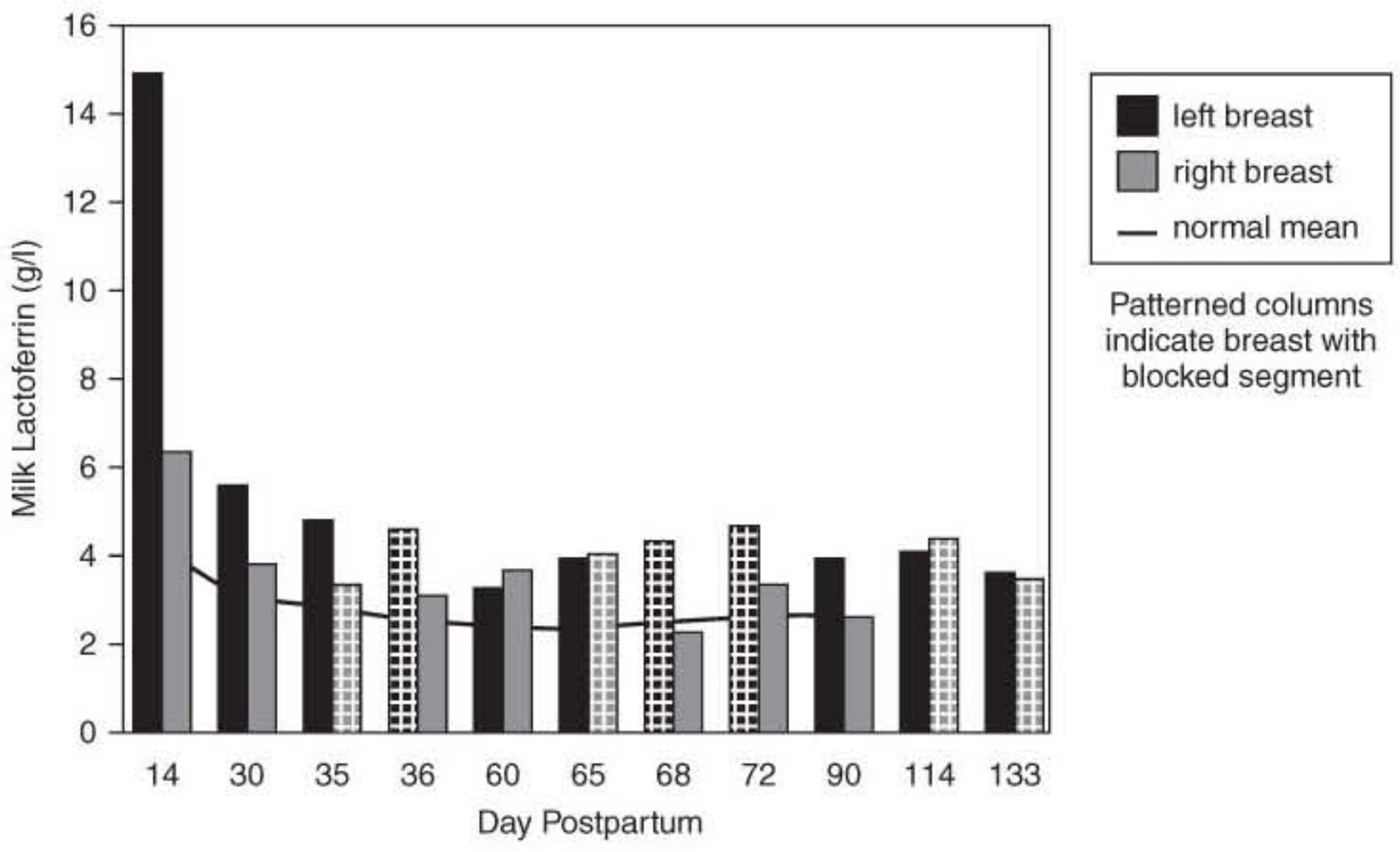

FIG. 1. Concentration of lactoferrin in breastmilk from M8 according to day postpartum (columns) compared to the normal mean lactoferrin of the other study mothers with asymptomatic breasts (solid line). Patterned columns (Days 35, 36, 65, 68, 72, 114, and 133) indicate a symptomatic breast with blocked duct(s). Non-patterned columns indicate an asymptomatic breast.

not detectable in the milk expressed for analysis, which most likely only occurred at the affected site. In contrast to the majority of the episodes of blocked duct(s) the low lactose and glucose concentrations on Day 133 reflect both an increase in breast permeability and a decrease in lactose synthesis.[14,15] The transient nature of some episodes of breast inflammation and the lack of certainty in being able to express milk from an area of inflammation, where the duct may be blocked, provide possible explanations for other unusual observations such as those in one study where a normal Na/K ratio was found even in the presence of observable breast inflammation and a raised tumor necrosis factor-alpha level in milk.[19]

It remains uncertain as to whether the absence of sIgA in the milk of M8 was a major contributing factor for her experiencing recurrent blocked duct(s). As sIgA is an anti-adhesive molecule, a deficiency of this Ig may have increased the likelihood of bacterial adhesion within the breast, causing local inflammation that was overcome with more frequent feeding and the subsequent increased flushing of milk. The recurrent nature of the problem is suggestive of a susceptibility of the breast to inflammation that may be related to the absence of IgA and is supported by another study where women who developed mastitis had lower levels of sIgA in their milk than the normal population.[5]

The only other mother in the study with a diagnosed medical condition (M21) was taking thyroxine replacement therapy for Hashimoto's thyroiditis, an autoimmune disease characterized by destruction of thyroid cells by various cell and antibody-mediated immune processes.[20] This mother experienced one episode of blocked duct(s) and four episodes of mastitis during this lactation and also reported a history of multiple recurrent episodes of mastitis with each of her previous three lactations. Although thyroiditis is one of a number of specific disorders associated with IgA deficiency, this was not the case with M21. However, she was observed to have significantly lower concentrations of sIgA in her breastmilk during the 90-day reference collection period, lending support to an association among low sIgA in breastmilk, increased stress, and susceptibility to breast inflammation.[5,8,9,21] The remaining episodes of blocked duct(s) detected during the study were associated with nipple trauma and oversupply, both conditions having been previously identified as predisposing factors for mastitis.[17,22]

The increased concentrations of lactoferrin in the milk of M8, particularly in the first 2 weeks postpartum, are of interest. There is evidence that sIgA acts synergistically both to enhance the bacteriostatic effect of lactoferrin by increasing lactoferrin's sequestration of iron from microorganisms and by binding to lactoferrin, enabling the protein to target microorganisms.[3] The increase in lactoferrin in the absence of sIgA may be suggestive of a compensatory effect. Variable patterns of compensatory increases of IgG and IgM antibodies have been reported in the milk from three women with IgA deficiency.[23] Although such analyses were not obtained for the milk from M8, her serum IgG and IgM were found to be at the higher end of the normal range. The associated high concentration of CRP in blood appears not to have been related to the breast as there was no obvious breast inflammation, although there was a very slight increase in urinary lactose excretion. This may be related to the increased CRP as increased breast permeability during lactation has been associated with acute systemic illness in the absence of obvious breast inflammation.[24]

Conclusions

As IgA deficiency has a high incidence in Caucasian populations it may be of value to consider investigating further those mothers with either recurrent blocked ducts or mastitis who also report a history suggestive of IgA deficiency, such as recurrent infections, drug allergy, or autoimmune or atopic disease.

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Disclosure Statement

No competing financial interests exist.

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